REMARKS

Claims 1-16 and 24-29 are currently pending in the application. Claims 1, 12-16, 24, 26, and 28 are in independent form. Applicant herein cancels claims 25, 27, and 29 without prejudice.

The Office Action holds that priority application USSN 10/015,123 does not support the recitation of "interferon-delta (IFN-δ)" in claims 1-11, 14-16, and 24-29 of the present application. In response thereto, Applicant has amended the claims and specification to read "interferon-gamma (IFN-γ)" and correct the typographical error of "IFN-δ" as in the priority application. Therefore, it is respectfully submitted that priority is correct as stated in the present application.

The Office Action holds that attempts to correct the instant disclosure of "interferon-delta (IFN-δ)" with "interferon-gamma (IFN-γ)" would be subject to a rejection under 35 U.S.C. §112, first paragraph for being new matter. The Office Action holds that the only disclosure of IFN-γ is on pages 25-26 of the instant specification in Table 1. The Office Action holds that there is no reference to IFN-γ in the context of anti-cancer treatment methods and assaying for IFN-γ is not the same as using IFN-γ in a NCM in anti-cancer treatment methods.

In response thereto, Applicant points out that there is no such compound that exists called IFN-δ in humans, IFN-δ only exists in pigs and cattle. One skilled in the art would automatically recognize that this is a typographical error. Furthermore, as stated in paragraphs [0094] and [0095]:

"***For the examples described herein***, pooled human peripheral blood buffy coats obtained from INCAN Blood Bank were incubated with phytohemagglutinin

(Murex, Dartford UK) and washed. The cells were incubated in serum-free medium (x-vivo 10, BioWhitaker) for twenty four hours. Batches were prepared from six blood donors and were screened by the INCAN Blood Bank for hepatitis B and C viruses, HTLV 1 and 2, and HIV. Following twenty-four hours of culture, the cultures were centrifuged, the supernatant was filtered through 0.2-micron filters, and the natural cytokine mixture was placed into vials. Activity of the batches of NCM of the present invention averaged 200 U/ml of IL-2 as determined by ELISA. Vials of the batches were stored at -70.degree. until use.

Cytokines were assayed using commercial ELISA kits (Quantikine.TM., R & D Systems, Inc., Minneapolis, Minn.)(See, Table I). Biological activity of the NCM of the present invention was confirmed using a murine cytotoxic T-cell line (CTLL-2), which was originally developed as an indicator of biological activity of IL-2." (Emphasis added)

In other words, the cytokines within the sample lots assayed from the batches produced were the same cytokines in the batches that were administered to patients in the INCAN study in the following examples and all batches were prepared from human sources. Applicants did not assay some other batches that were not part of the study. There is no reason to believe that any other IFN was used other than IFN-γ. If the lots of NCM assayed that were produced specifically to be administered to patients contained IFN-γ (and they could not possibly contain IFN-δ as stated above), then the patients received IFN-γ in their treatments. The recitation of IFN-δ was an obvious error and one skilled in the art would automatically recognize that IFN-γ was in fact administered based on the assay results in Table 1. Reconsideration of the rejection is respectfully requested.

The application is objected to because of failure to comply with sequence disclosures. In response thereto, Applicant has amended the specification and

included a sequence listing along with amendment directing its entry into the specification as required. Reconsideration of the objection is respectfully requested.

The specification is objected to because of the use of trademarks and embedded hyperlinks and/or other form of browser-executable code. In response thereto, Applicant has amended the specification to comply with these requirements. Reconsideration of the objection is respectfully requested.

Claims 2-9, 13, and 16 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Office Action holds that there is insufficient antecedent basis for "said administering step" in claims 2-9. Applicant points out that claim 1 reads "A method of immunotherapy to treat cancer by ***administering*** an effective amount of a natural cytokine mixture (NCM)..." (emphasis added). This is a step of administering since it is an active step in a method claim. Therefore, there is support for "said administering step" in claims 2-9.

The Office Action also holds that claims 13 and 16 are indefinite in the recitation of "a synergistic anti-cancer treatment/method" because this "synergistic" limitation is relative in nature. The Office Action holds that it appears that the "synergistic anti-cancer treatment" is simply adding "an effective amount of cyclophosphamide and an effective amount of indomethacin/NSAID" in combination with a natural cytokine mixture and/or with other forms of immunotherapy. The common dictionary meaning of "synergistic" or "synergy" is "the interaction of two or more agents or forces so that their combined effect is greater than the sum of their individual effects." This is not indefinite, one skilled in the art can observe that the

effects of administration of the compounds of the present invention alone versus together gives unexpected results such that the effects together are greater than the sum of the effects alone. This is precisely the definition of "synergistic". Therefore, Applicant has amended claims 13 and 16 to recite the steps of producing an activity greater than the individual activities of CY and NSAID (and the NCM). Support for these amendments can be found in paragraph [0121]:

"In four patients **a dose of the NCM was given that was considered inactive** (See, FIG. 10, 15 units column) **in conjunction with INDO and CY**. No survivals were observed, yet **two patients had minor response** (<50%, but >25% tumor shrinkage) and **all four showed moderate pathological changes** in the tumor specimen with tumor reduction and fragmentation as well as lymphoid infiltration (See, Table IV). **INDO** can increase lymphoid infiltration and tumor reduction in some patients (See, Panje, 1981, and Hirsch, et al., 1983), but it **has not been accepted clinically as a useful therapy in H&N SCC. Similarly, CY at this dose is not considered clinically active in H&N SCC. The activity of INDO and CY alone can be considered surprising in the magnitude and type of tumor response. INDO and CY are considered as a synergistic combination for employment with other forms of immunotherapy**." (Emphasis added)

In other words, the activities of NCM, INDO, and CY at these doses were expected to be non-existant. The evidence shown in the application proved otherwise, indicating that a synergistic effect was present and the activities of the compounds together was greater than the individual activities. This is not experienced at just a single dosing level but at any dosing level. One skilled in the art can tell what is a synergistic effect with the compounds of the present invention at any dosing level.

Reconsideration of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claims 24-29 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Office Action holds that the present claims are directed to a method of eliciting an immune response to exogenous tumor antigens by administering NCM with or without CY and/or INDO; however, the specification as filed does not provide sufficient enabling description for elicting an immune response without administering any antigen. In response thereto, Applicant has amended the claims to require the step of administering exogenous tumor antigens to conform with the election of exogenous tumor antigens. Applicant has canceled claims 25, 27, and 29 without prejudice. Reconsideration of the rejection is respectfully requested.

Claims 1-13 and 24-29 stand rejected under 35 U.S.C. § 102(b), as being anticipated by Meneses, et al. Specifically, the Office Action holds that Meneses, et al. teaches a method of treating head and neck squamous cell carcinoma (H&NSCC) comprising administering an NCM comprising IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, TNF-α, CSF, IFN-γ, and effective amounts of CY and INDO, in which 150 units of IL-2 equivalence by ELISA is administered. The Office Action further holds that it is noted that although the prior art does not explicitly teach "a synergistic anti-cancer treatment" or "a method of eliciting an immune response to tumor antigens" *per se*, given the same or nearly the same method step of administering an NCM plus CY and INDO for treating H&NSCC, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by Meneses, et al., as applied to the claims, is respectfully requested. Anticipation has always been

held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

In Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986) it was stated: "For prior art to anticipate under §102 it has to meet every element of the claimed invention."

In Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989) it was stated: "Every element of the claimed invention must be literally present, arranged as in the claim."

Applicant has amended currently pending independent claim 1 to further clarify the method of cancer treatment by administration of the NCM. In particular, Applicant has added the steps of maturing immature dendritic cells, and allowing presentation by resulting mature dendritic cells of exogenous antigens. No new matter has been added and the amendment is still within the elected species. Support for these amendments can be found in paragraphs [0040] and [0041] of the present invention (emphasis added):

[0040] **Thus, the present invention provides for unblocking immunization at a regional lymph node by promoting differentiation and maturation of immature dendritic cells in a regional lymph node and thus allowing presentation by resulting mature dendritic cells of small peptides**, generally nine amino acids in length to T cells to gain immunization of the T cells. Additionally, induction of mature dendritic cells is required. Finally, mobilization of peripheral blood T-lymphocytes in T-lymphocytopoenic patients in the presence of induction of naive T cells capable of responding to dendritic cells presenting endogenous tumor peptides is desired. (See, Sprent, et al, Science, Vol 293, Jul. 13, 2001, pgs 245-

248).

[0041] In view of the above, **the key mechanistic features of the present invention are the in vivo maturation of dendritic cells resulting in effective peptide antigen presentation**. Based on the examples presented below, increases in CD45 RA positive naive uncommitted T cells have been found. With antigen, this leads to T and B cell clonal expansion, creating immunity in the patient. The resulting infiltration into tumors by hematogenous spread leads to robust tumor destruction. The result, as found in the data below, is increased survival due to immunologic memory. (See, Sprent et al, cited above).

Meneses, et al. does not disclose the required steps of maturing immature dendritic cells or allowing presentation by resulting mature dendritic cells of exogenous antigens. There is no mention at all of dendritic cells or antigens. It was not known at the time of Meneses, et al. that the NCM could mature immature dendritic cells and Meneses, et al. provides no evidence of such a process occurring. In contradistinction, the present invention provides evidence of immature dendritic cells maturing as a result of the NCM, such as that shown in Figure 11. Effective mature dendritic cells that can present exogenous antigen are required for the treatment of cancer by immunotherapy of the NCM.

With respect to independent claims 12 and 13, Meneses, et al. does not disclose a treatment of CY and INDO/NSAID alone without administration of the NCM. Furthermore, Applicant has amended the claims as stated above to recite additional method steps that are not disclosed by Meneses, et al. Independent claim 13 requires a synergistic anti-cancer treatment method including the step of producing an activity greater than the individual activities of CY and NSAID. There is no evidence in Meneses, et al. that CY and INDO behave synergistically as opposed

to that shown in the present invention as discussed above. Claims 24-29 have been amended to require the step of administering an effective amount of exogenous antigens. Meneses, et al. does not disclose administering any antigens.

Therefore, since Meneses, et al. does not disclose the required steps of maturing immature dendritic cells, allowing presentation by resulting mature dendritic cells of exogenous antigens, administering CY and INDO/NSAIDS alone, a synergistic anti-cancer treatment producing greater activity than individual components, or administering exogenous antigens as set forth in the presently pending independent claims, the claims are patentable over Meneses, et al. and reconsideration of the rejection is respectfully requested.

Claims 1-11, 14-16, and 24-29 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Meneses, et al. in view of U.S. Patent Application Publication No. 20030007955 to Rees, et al. Specifically, the Office Action holds that Meneses, et al. teaches as described above. Meneses, et al. does not teach IFN-delta, GM-CSF, and G-CSF in the NCM. However, the Office Action holds that would have been obvious to one skilled in the art to include these components for treating cancer because these are well-known therapeutic proteins for treating cancer as exemplified by Rees, et al. The Office Action holds that Rees, et al. teaches a method of treating a squamous cell carcinoma comprising administering a mixture of therapeutic proteins selected from a list of cytokines that include IL-1, IL-2, IL-6, IL-8, IL-12, IFN-delta, TNF-α, GM-CSF, and G-CSF. Therefore, the Office Action holds that given that both Meneses, et al. and Rees, et al. teach treating head and neck cancer using a cytokine mixture, it would have been obvious to one skilled in the art to include IFN-delta as taught by Rees, et al. in the cytokine mixture as taught by Meneses, et al. for the same purpose of treating head and neck cancer because there is a finite number of IFN types to choose from.

Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over Meneses, et al. in view of Rees, et al. is respectfully requested.

As stated above, Meneses, et al. does not disclose each of the steps as required by the currently pending independent claims. Combining Meneses, et al. with Rees, et al. would still not arrive at the present invention. Rees, et al. does not disclose any of the missing steps from Meneses, et al. as described above.

Since neither the cited references alone or in combination with knowledge in the art suggest the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

Claims 1-2, 10-16, and 24-29 of this application have further been rejected as unpatentable based on provisional non-statutory obviousness-type double patenting over Patent No. 6,977,072. As noted in the Office Action, these rejections can be readily overcome by the filing of a terminal disclaimer in compliance with 37 C.F.R. 1.321(c) or (d). Applicant stands ready to provide the appropriate terminal disclaimer upon the indication of the allowance of the pending claims.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above, and the prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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